2015-1693

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

INTELLIGENT BIO-SYSTEMS, INC.,

Appellant,

v.

ILLUMINA CAMBRIDGE LTD.,

Appellee.

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in No. IPR2013-00517

REPLY BRIEF OF APPELLANT INTELLIGENT BIO-SYSTEMS, INC.

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November 24, 2015

CERTIFICATE OF INTEREST

Counsel for Appellee certifies the following:

1. The full name of every party or amicus represented by me is:

Intelligent Bio-Systems, Inc.

2. The full name of the real party in interest represented by me is:

Intelligent Bio-Systems, Inc.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curie represented by me are:

QIAGEN North American Holdings, Inc.; QIAGEN US Finance Holdings (Luxembourg) SARL; QIAGEN N.V.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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Dated: November 24, 2015

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TABLE OF ABBREVIATIONS AND REFERENCES

IBS	Intelligent Bio-Systems, Inc.
Illumina	Illumina Cambridge Ltd.
The Board	United States Patent and Trademark Office, Patent Trial and Appeal Board
IPR	*inter partes* review
SBS	Sequencing by synthesis
'537 patent	U.S. Patent No. 7,566,537
Greene & Wuts	*Protecting Groups in Organic Synthesis* (Theodora W. Greene & Peter G. M. Wuts eds., John Wiley & Sons, Inc. 3rd ed. 1999)
Ju	U.S. Patent No. 6,664,079
Kit	Kit, Ann. Rev. Biochem 32:43 (1963)
Knouzi	Knouzi et al., Bull. Soc. Chim. Fr., 815-819 (1985)
Lee	Lee et al., Proc. Natl. Acad. Sci. 78:2838 (1981)
Loubinoux	Loubinoux et al., 44 Tetrahedron 6055 (1988)
Mag and Engel	Mag & Engel, 17 Nucleic Acids Research 5973 (1989)
Mungall	Mungall et al., 40 J. Org. Chem. 1659 (1974)
Stanton	PCT Publication WO 02/21098
Tsien	PCT Publication WO 91/06678
Zavgorodny	Zavgorodny et al., 32 Tetrahedron Letters 7593 (1991)

ARGUMENT IN REPLY

Illumina's opposition brief is striking for what it does *not* say about the infirmities in the PTAB's decision. In particular, IBS's opening brief identified three manifest legal errors by the Board, each of which warrants reversal: (1) the Board's failure to use the invention claimed in the '537 patent to assess the skilled artisan's reasonable expectation of success; (2) the Board's failure to credit the skilled artisan with the ordinary creativity mandated by the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 378 (2007) and corresponding Federal Circuit precedent; and (3) the Board's imposition of a heightened "guarantee of success" standard for a skilled artisan. IBS also explained, in detail, how the Board compounded these three separate, reversible legal errors by seriously misreading the prior art that renders obvious the challenged claims of the '537 patent.

Yet Illumina makes no serious effort to respond substantively to these points, or otherwise to defend the PTAB decision on its merits. Instead, Illumina tries to dodge the Board's analysis (and IBS's arguments on appeal) by: (1) relying on purported procedural objections that do not substantively address (let alone rebut) IBS's arguments; (2) miscasting the Board's legal errors as "factual findings" entitled to deference, which plainly they are not; and (3) inviting this Court to affirm on the grounds of alternative, complex and disputed issues of fact

not considered in the Board's decision on appeal. Indeed, Illumina's reliance on these disputed alternative bases is telling for an appellee that contends the Board acted correctly in the proceedings below.

In short, Illumina's failure to substantively address (much less vigorously defend) the Board's faulty analysis warrants reversal. In the alternative, this court should vacate and remand the Board's decision, so that the Board may assess the obviousness of the '537 patent under the correct legal framework.

I. The Board Substantively Considered IBS's Reply Materials, Which Did Not Exceed the Proper Scope of a Reply

Illumina contends that IBS "cannot rely" in this *de novo* appeal on arguments and evidence that IBS presented to the Board on reply, and which the Board substantively considered in issuing its Final Written Decision. Illumina Br. at 19; JA16-18. Indeed, Illumina repeatedly relies on this narrow procedural objection, rather than mount the full-throated, substantive defense of the Board's decision that one would normally expect to see from an appellee. *See, e.g.,* Illumina Br. at 23-30, 45, 48, 51, 52, 54, 57, 60.

Illumina's objection to IBS's reply materials ignores the plain fact that the Board *did* consider the materials in rendering its Final Written Decision. JA16-18. IBS submits that the Board erred by not invalidating the '537 patent in light of the arguments and evidence presented in IBS's Petition and in its reply materials; but as a procedural matter, the reply materials are properly before this court on appeal.

Accordingly, and contrary to Illumina's suggestion, they may be considered by this court in evaluating the Board's decision for error.

Moreover, Illumina's core complaint – that IBS's timely submission of its reply materials somehow "deprived the Board of Illumina's response," Illumina Br. at 23, 28[1] – is quite incorrect. In its Institution Decision, the Board found that IBS's Petition made out a *prima facie* case of obviousness based in part on the combination of either Tsien or Ju with Zavgorodny. JA160-176. In particular, the Board found that IBS's Petition made out its *prima facie* case because the '537 patent "describes a method of labeling nucleic acids," and also separately "describes nucleic acid sequencing methods." JA162. Likewise, Ju and Tsien each "describes a process of labeling, and ultimately sequencing a nucleic acid molecule." JA166, 169. In other words, from the outset of the proceedings, the

[1] Illumina also argues that IBS's reply materials submitted to the Board "did not comply with the Board's rules of practice." Illumina Br. at 23. IBS's opening brief explained, in detail, how Illumina's Patent Owner Response injected specific responsive arguments into the case, which IBS properly rebutted with its reply materials that were consistent with its Petition. *See* IBS Br. at 56-58; *see also Belden, Inc. v. Berk-Tec LLC*, No. 2014-1575, -1576, 2015 WL 6756451, at *11 (Fed. Cir. Nov. 5, 2015) ("Evidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case."). Moreover, as Illumina acknowledges (Illumina Br. at 27), "[a] petitioner is not expected to anticipate, in its petition, every counterargument a patent owner might make in response." *St. Jude Med., Cardiology Div., Inc., v. The Board of Regents of the Univ. of Mich.*, IPR2013-00041, 2014 WL 1783276, at *20 (P.T.A.B. May 1, 2014). Likewise, IBS properly cited to its reply expert declarations in its reply brief before the Board. Accordingly, to the extent the Board did not consider IBS's reply materials in reaching its Final Written Decision, the Board abused its discretion.

Board understood both the scope of IBS's Petition, and that Ju and Tsien were directed to general processes of labeling and not (as Illumina now contends) only the narrower teachings of sequencing by synthesis.

In addition, after IBS submitted its reply brief and the supporting declarations and exhibits of Drs. Branchaud and Metzker, Illumina deposed both experts at length on their reply declarations and supporting exhibits (JA7207; JA7493); filed written observations on those cross-examinations (JA458); and moved to exclude the experts' reply declarations and supporting exhibits (JA433). On this record, Illumina has no basis to complain about the Board's decision to consider IBS's reply materials. Indeed, the Federal Circuit recently recognized this precise point in *Belden*, 2015 WL 6756451, in which the court rejected the same argument that Illumina makes here regarding IBS's reply materials.

In *Belden*, a petitioner introduced expert testimony for the first time with its reply, and the patent owner objected by saying (as Illumina does here) that "it had no opportunity to respond" to the new material. *Id.* at *3. The Federal Circuit rejected the patent owner's objection, noting that the "the prior art itself, together with the Petition, sufficed to supply a prima face case of obviousness – as confirmed by the Institution Decision." *Id.* at *11. The court in *Belden* further noted that the patent owner – by deposing the new expert, submitting observations on the deposition, and moving to exclude the expert – received "a meaningful

opportunity to respond to the grounds of rejection." *Id.* at *14. A similar result obtains here; and so Illumina's procedural objection to this court's consideration of IBS's reply materials in this *de novo* appeal is without merit.[2]

II. The Board Erred As a Matter of Law by Failing to Invalidate the Challenged Claims as Obvious

A. The Board Erred By Failing to Measure Reasonable Expectation of Success Against the Claimed Invention

As a matter of law, a skilled artisan's reasonable expectation of success must be measured by the *claimed invention*, and not by the prior art underlying the obviousness analysis. *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1282, 1292 (Fed. Cir. 2013) ("[T]he person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention."). In its opening brief before this court, IBS explained that the challenged claims of the '537 patent are not limited to SBS, and so nothing in those claims require the azidomethyl group to be removed

[2] Illumina's cited cases are readily distinguishable. Illumina Br. at 25. In two of them, the Board did *not* exclude any evidence as improper reply arguments. *See Facebook, Inc. v. Software Rights Archive, LLC*, IPR2013-00478, 2015 WL 470597, *22 (P.T.A.B. Feb. 2, 2015); *CBS Interactive, Inc. v. Helferich Patent Licensing LLC*, IPR2013-00033, 2013 WL 8699189 (P.T.A.B. Aug. 9, 2013). In the other three cases cited by Illumina, the Board excluded new claim constructions, new testing data, and entirely new interpretations of the prior art. *See Toyota Motor Corp., v. Amer. Vehicular Sciences LLC*, IPR2013-00424, 2015 WL 183909, *10-11 (P.T.A.B. Jan. 12, 2015); *The Scotts Co. LLC v. Encap, LLC*, IPR2013-00110, 2014 WL 2886290, *3 (P.T.A.B. June 24, 2014); *Corning, Inc. v. DSM IP Assets B.V.*, IPR2013-00047, 2014 WL 1783279, *8-10 (P.T.A.B. May 1, 2014). The Board's decisions in these cases are inapplicable to the expert declarations and supporting exhibits that IBS provided to the Board, solely to respond to the arguments Illumina made in its Patent Owner Response.

quantitatively – only that it be removable. IBS Br. at 39-40.[3] Indeed, in the proceedings below, Illumina never sought a claim construction that would require quantitative removal of the azidomethyl group – because there is no support in the claims, specification, or prosecution history of the '537 patent for such a claim construction.

However, the Board erred by requiring IBS to show that a skilled artisan would have expected Zavgorodny's azidomethyl group to be removed quantitatively, even though the challenged patent claims do not contain such a requirement. JA14; JA21. In other words, the Board erred as a matter of law by essentially engrafting, into the challenged patent claims, a quantitative removal requirement that is not in the claims. IBS Br. at 37-40.

Illumina's Opposition makes no serious effort to rebut any of these points. Instead, Illumina principally tries to mischaracterize the Board's decision on this issue, suggesting that the Board hinged its reasoning not on the skilled artisan's reasonable expectation of success, but rather on the motivation to combine the prior art references. Illumina Br. at 42-43 (discussing the Board's analysis in light of a "reason to combine the prior art"). This gloss completely ignores the Board's

[3] As noted in Section I, *supra*, the Board's Institution Decision confirms that the "'537 patent describes a method of labeling nucleic acids," and separately "also describes nucleic acid sequencing methods." JA 162.

decision, which expressly grounded its obviousness analysis in the artisan's "reasonable expectation of success." JA9 (quoting *KSR*).

Illumina also incorrectly contends that "[e]ven if the Board's findings were based on a lack of expectation of success, the Board's findings are proper in light of the asserted prior art." Illumina Br. at 44. As noted above, that assertion is wrong as a matter of law, because the expectation of success is measured by the *patent claims*, not the *prior art*. Illumina's cases on this point are not to the contrary. Illumina Br. at 44. In *Amgen, Inc. v. F. Hoffman-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009), the court assessed the success by recourse to the claims, not the prior art. And *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988) predates *KSR*'s teachings.

Moreover, even if the Board *had* grounded its analysis in an artisan's motivation to combine, such motivation is *still* measured against the challenged patent claims, not the prior art. *See In re Icon Health and Fitness, Inc.*, 496 F.3d 1374, 1381-82 (Fed. Cir. 2007) (assessing whether the reference taught away by reference to the patent claims); *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952, 962 (Fed. Cir. 2014) (reversing district court's decision finding no motivation to combine because "the district court erred by failing to take into account the full scope of the [asserted] patent claims"). In short, even under Illumina's misreading

of the Board's decision, an error of law exists that infects the Board's obviousness analysis, mandating reversal.

B. The Board Erred by Failing to Take into Account the Creativity of a Person of Ordinary Skill in the Art

Nothing in the challenged claims of the '537 patent require Zavgorodny's azidomethyl group to be quantitatively cleaved. However, to the extent that a reasonable expectation of such high cleaving efficiency is required, the '537 patent *itself* discloses that such cleavage conditions are routine in a labeling or sequencing method. The '537 patent plainly states that choosing cleavage conditions for the 3′OH group was "conventional" for a skilled artisan, and that "[t]he process used to obtain the 3′OH group can be any suitable chemical or enzymic reaction." JA41 at 7:65 to 8:4.[4] And other Board panels have relied on this exact portion of the specification in finding that the patent "suggests that choosing cleavage conditions for the 3′-OH group were conventional to one of ordinary skill in the art." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, IPR2013-00128, 2014 WL 3736339, *10 (P.T.A.B. July 25, 2014); *see also Intelligent Bio-Systems, Inc.*

[4] Illumina suggests that the '537 patent discloses "that cleavage conditions could be varied **only after** the azidomethyl group had been selected for SBS." Illumina Br. at 57 (emphasis in original). The patent, however, contains no such disclosure.

v. Illumina Cambridge Ltd., IPR2013-00266, 2014 WL 5490579, *10 (P.T.A.B. October 28, 2014).[5]

Accordingly, the challenged patent claims do not contain the quantitative cleavage requirement that the Board read into them.[6] But even if the claims did contain that requirement, then the Board still erred as a matter of law by not infusing the skilled artisan with the "ordinary creativity" and skill to optimize Zavgorodny's removal conditions to meet such a cleavage requirement. *KSR*, 550 U.S. at 421; *In re Icon*, 496 F.3d at 1382 ("[W]e do not ignore the modifications that one skilled in the art would make to a device borrowed from the prior art"). That is particularly so because – in the chemical arts – the "ordinary creativity" of a skilled artisan would include the ability to optimize conditions of the type

[5] Illumina complains that these other Board decisions "are not of record in this IPR." Illumina Br. at 55. First, the one decision was discussed on the record at the oral hearing (JA609 ll. 9-25), and the other decision was not published until after the Board's oral hearing. Second, this court of course may take judicial notice of a relevant Board decisions even if they are not in the record on appeal. *Function Media, L.L.C. v. Google, Inc.*, 708 F.3d 1310, 1316 n.4 (Fed. Cir. 2013) ("It is proper to take judicial notice of a decision from another court or agency at any stage of the proceeding, even if it was not available to the lower court."). This is particularly so where (as here), the patents are related, have the same priority date, and share a common specification.

[6] As IBS discussed in its opening brief before this court, Illumina cannot represent to the public in its patent that choosing suitable cleavage conditions would be routine, and then – at the same time – argue that a skilled artisan would *not* have been able to develop such suitable cleavage conditions. *See* IBS Br. at 45 – 46 (collecting cases).

disclosed by Zavgorodny. *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1349, n.2 (Fed. Cir. 2009) ("[O]ne skilled in the art would have known how to vary the [chemical] concentration or other parameters in order to achieve the [claimed result]. Such experimentation is routine and cannot render an otherwise obvious claim valid."); *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (determining "where in a disclosed set of percentage ranges is the optimum combination of percentages" is *prima facie* obvious); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990) (finding the amount of eluent was "a matter of routine optimization in the pertinent art").

Illumina's response on this dispositive legal issue is abbreviated, to put it mildly. Illumina only (1) points to the Board's quotation of *KSR* (*see* Illumina Br. at 51 (citing JA 9)), and (2) suggests that the presence of the *KSR* quote necessarily means that the Board vested the artisan with the necessary ordinary creativity. Illumina Br. at 51. But there is nothing in the Board decision showing that the Board – as precedent requires – in fact considered "the knowledge of one of skill in the art appropriately." *Randall Mfg. v. Rea*, 733 F.3d, 1355, 1363 (Fed. Cir. 2013). Without evidence that the Board correctly applied the controlling legal standard, a passing citation to that legal standard is not sufficient on this *de novo* appeal. *See, e.g., Arrowpoint Capital Corp. v. Arrowpoint Asset Mgmt.*, LLC, 793 F.3d 313,

322-23 (3d Cir. 2015) (vacating and remanding decision where "the District Court cited the correct standard," but "did not then appear to apply that standard").

In short, skilled artisans would have used "ordinary creativity" to optimize, if necessary, the cleavage conditions identified in Zavgorodny. The Board's failure to account for and apply that principle is legal error that warrants reversal.

C. The Board Erred by Applying Too Strict a Standard for Expectation of Success

"The expectation of success need only be reasonable, not absolute." *Pfizer Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("simply because the formation and properties of [a new compound] must be verified through testing" does not mean that the compound satisfies the test for patentability); *see also Hoffmann-LaRoche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."). Yet, in derogation of that legal standard, the Board improperly required IBS to show that – in order to achieve a reasonable likelihood of success – a skilled artisan "would have [to] **expect**[] Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative deblocking requirement." JA13-14 (emphasis added); *see also* JA21 (same observation regarding Ju). In its opening brief, IBS explained how the imposition of this new, unduly strict standard for expectation of success contravened Federal Circuit precedent. IBS Br. at 48-50 (collecting cases).

Illumina's response – buried in one paragraph of its brief – is no response at all. Illumina Br. at 47. Illumina does not cite (let alone try to distinguish) this court's holdings in *Pfizer* or *Hoffmann-LaRoche* on the correct legal standard for expectation or success. Nor does Illumina attempt to defend the Board's erroneous formulation and application of the legal standard. Instead, Illumina contends, without citation to authority, that the Board's incorrect formulation of the legal standard "should be treated as factual findings, which are reviewed for substantial evidence." Illumina Br. at 48.[7] This argument runs afoul of controlling precedent, and should be rejected.

The issue of whether the Board formulated and applied a correct legal standard is a question of law that this court reviews *de novo*. *Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.*, 786 F.3d 960, 964-65 (Fed. Cir. 2015) (vacating and remanding TTAB decision because the Board applied an incorrect legal standard). And where – as here – the Board "appeared to apply an erroneous legal standard," the court "must set aside the decision and remand for further proceedings" under

[7] Illumina also laconically observes in a footnote that the Board's decision quotes language from *KSR* regarding the reasonable expectation of success, which Illumina contends insulates the Board from failing to apply the *KSR* standard it cited. *See* Illumina Br. at 47 n.5 (citing JA9). Of course, the point here is that the "near certainty" standard that the Board imposed is contravened by *KSR* and Federal Circuit precedent. In any event, citation to a legal standard does not substitute for the Board's adherence to, and correct application of, that standard. *See, e.g.*, *Arrowpoint Capital Corp.*, 793 F.3d at 322-23.

the correct legal standard. *Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1152-53 (Fed. Cir. 2007) (vacating and remanding special master's decision for new determination "that applies the correct legal standard to the record as a whole"). This rule applies with equal force to whatever facts are derived from application of the Board's incorrect legal standard, because such factual findings "cannot be allowed to stand" on appeal. *Id.* at 1152 (internal citations omitted); *accord*, *e.g.*, *Pullman-Standard v. Swint*, 456 U.S. 273, 292 (1982) (noting that it is "elementary" that "where findings are infirm because of an erroneous view of the law, a remand is the proper course unless the record permits only one resolution of the factual issue").

In short, Illumina is wrong to suggest that incorrect legal standards can be mislabeled as "factual findings," and then shrugged off as somehow warranting deference.[8] Moreover, any "facts" that are derived from the Board's incorrect formulation of the standard for reasonable expectation of success are themselves

[8] In *In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1378 (Fed. Cir. 2007), the Federal Circuit described the types of factual findings that – in an obviousness challenge – are subject to deference, as including "the scope and content of the prior art, the level of ordinary skill in the art at the time of the invention, objective evidence of nonobviousness, and differences between the prior art and the claimed subject matter." Suffice to say that the Board's formulation of its expectation of success standard, in this case, cannot fairly be characterized as a "factual finding" akin to the examples set forth in *Icon*.

subject to vacatur and remand, so that the Board may make new findings "under the correct standard in the first instance." *Walther*, 485 F.3d at 1152.

III. The Board's Decision Lacks Substantial Evidentiary Support

A. The Prior Art Provides a Reasonable Expectation that Zavgorodny's Conditions Would Result in Quantitative Cleavage

IBS presented evidence that a person of ordinary skill in the art would have reasonably expected success in using Zavgorodny's deblocking conditions to quantitatively cleave an azidomethyl protecting group. As IBS asserted in its petition and the Board recognized in its institution decision, Zavgorodny's teachings that its nucleosides are useful as "specifically blocked synthons" and "the fact that azidomethyl group is cleavable from the nucleoside under specific and mild conditions" suggests that it would meet Tsien's and Ju's requirements for a protecting group. JA167-68; JA172; JA131-134; JA144-46. Both IBS and Illumina agree that the Board primarily relied on Loubinoux to support its conclusion that an ordinary artisan would not have expected Zavgorodny's azidomethyl group to meet Tsien's and Ju's quantitative deblocking requirement.[9] JA13; JA21; Illumina Br. at 32. However, the Board's finding that "the prior art suggests that an ordinary artisan would not have expected Zavgorodny's

[9] The Board also relied on Greene & Wuts to support its position that an ordinary artisan would have expected lower efficiency than that disclosed in Loubinoux for the 3′ hydroxyl of Zavgorodny "because phenol is a better leaving group." JA13.

azidomethyl group to be removed quantitatively" is not supported by substantial evidence. JA14.

Critically, as IBS point out in its opening brief, the Board mistakenly relies on the isolated pure product ***yields*** of Loubinoux as an indicator of the ***efficiency*** of Zavgorodny's cleavage conditions. IBS Br. at 51-52; JA1894-95 at ¶ 20. Notably, Illumina does not challenge that efficiency is the proper measure. Rather, Illumina argues that there are other reasons that ***yields*** may not be quantitative. Illumina Br. at 59. But this just emphasizes why a person of ordinary skill in the art would not use yields to predict efficiency. Illumina also asserts that "the evidence shows that the azide-to-amine reaction on a nucleotide results in side products." Illumina Br. at 59 (citing JA7193). However, Illumina's argument is irrelevant to whether Zavgorodny's conditions would result in unwanted side products. Illumina's evidence does not involve a Staudinger reaction or even an azidomethyl group bound to a 3′ oxygen like Zavgorodny, but rather involves an azido group directly bound to a 3′ carbon. *See* discussion of Ex. 2152 at JA482-83 (citing JA1897 at ¶ 24).

Using the right metric (efficiency), IBS provided evidence that Zavgorodny's conditions (triphenylphosphine) would result in quantitative cleavage. In particular, IBS provided Knouzi, which Loubinoux cites for its triphenylphosphine reaction conditions. JA974 at n.4, JA987; JA1895 at ¶ 21.

Knouzi teaches that "reaction of azides with one equivalent of triphenylphosphine in the presence of a slight excess of water in THF leads ***quantitatively*** to the corresponding primary amines." JA2232; JA1895 at ¶ 21. In response, Illumina argues that Knouzi (and other references relied on by IBS such as Mag and Engel) do not involve nucleotides, and that IBS has not shown why these references would be suitable for sequencing. Illumina Br. at 48-49. However, IBS uses Knouzi to rebut the assertion that Loubinoux and Greene & Wuts would indicate that Zavgorodny's conditions would be inefficient. Neither Loubinoux nor Greene & Wuts involves nucleotides or sequencing reactions. Yet, the Board and Illumina take IBS to task for relying on similar references. Here, Knouzi completely undermines the Board's reliance on Loubinoux as indicative of the cleavage efficiency of Zavgorodny's conditions.

Illumina further argues that "the lower cleavage efficiencies for nucleotides [as compared to nucleosides] found in the [Mungall reference] support the expectation that Zavgorodny's cleavage conditions would not proceed with the nearly 100% efficiency required by Tsien and Ju." Illumina Br. at 49. Illumina's argument is both misleading and irrelevant. First, Mungall like Loubinoux reports ***isolated product yields*** not "***cleavage efficiencies***" as asserted by Illumina. JA2995. Second, Mungall describes different purification procedures for the nucleoside experiments as compared to the nucleotides. *See, e.g.*, JA2995

(compare procedure for compound 1b to procedure for compound 2). Thus, Mungall just reaffirms that isolated product yields would not be considered as indicative of cleavage efficiencies and that yields below 100% would not dissuade a skilled person from using azidomethyl as a protecting group.

Accordingly, when the record is viewed as a whole, the Board's decision that Zavgorodny's conditions would result inefficient cleavage of the azidomethyl group for sequencing lacks substantial evidentiary support.

B. A Person of Ordinary Skill in the Art Could Have Optimized Zavgorodny's Conditions

Contrary to Illumina's argument, IBS's petition is not limited to Zavgorodny's cleavage conditions. Illumina Br. at 52. IBS did not expressly rely on the exemplary conditions noted by Zavgorodny (triphenylphosphine in aqueous pyridine at 20ºC). JA861. Rather, IBS's petition and its expert rely on Zavgorodny's statement that azidomethyl "can be removed under very specific and mild conditions," the structural similarity of azidomethyl to the protecting groups discussed in Ju and Tsien, and the skilled artisan's "general skill in synthetic chemistry." JA132-33; JA145-46; JA1141-42 at ¶¶ 56-57, 60; JA1148-49 at ¶¶ 80-81, 84. As discussed above, one of ordinary skill would modify Zavgorodny's conditions to optimize for higher efficiency if necessary. *See supra*, pp. 9-10.

As evidence that one of skill in the art could have modified Zavgorodny's cleavage conditions, IBS identified TCEP (tris(2-carboxyethyl)phosphine) as a

possible cleaving agent. Illumina argues that IBS did not explain with "specificity" why a skilled artisan would have been drawn to TCEP, and that using TCEP to reduce an azide was new as of the '537 patent's effective filing date. Illumina Br. at 53-54. Illumina is wrong on both counts. First, IBS explained that a skilled artisan would have been drawn to TCEP because it follows the same chemical mechanism as the triphenylphosphine identified by Zavgorodny. JA396-97; JA1892-94 at ¶¶ 14-18. Second, using TCEP to reduce an azide was ***not*** new as of the effective filing date, IBS relied on the Stanton reference dated ***before*** the effective filing date of the '537 patent to show that TCEP had been used to reduce an azide to an amine. JA1973 at JA2059-60, Scheme 11; JA1893-94 at ¶ 18.

Moreover, Illumina's point regarding Stanton is baseless. Stanton does not indicate that the reaction with TCEP would produce "an amine that could attack the phosphate ester linkages comprising the DNA in Tsien and Ju's SBS methods." Illumina Br. at 54. Stanton discloses the reduction of an azido group to an amine, not the reduction of an azidomethyl ether (as in the Ju/Tsien-Zavgorodny combination). JA2059-60, Scheme 11. Unlike the reduction of the azido to an amine in Stanton, the reduction of an azidomethyl ether would result in an unstable intermediate that would rapidly hydrolyze to a hydroxyl group. JA1892 at ¶ 14; JA481. Thus, contrary to Illumina's argument, there would be no amine group to "attack the phosphate ester linkages" in Ju's and Tsien's methods.

IV. This Court Should Decline to Address Illumina's Other Grounds for Affirmance as Requiring Fact-Finding and as Unsupported by the Record as a Whole

Perhaps because Illumina understands that the Board's decision is not supported by substantial evidence, Illumina devotes a large portion of its arguments to alternative factual grounds for affirmance neither addressed by the Board nor supported by the record. *See, e.g.*, Illumina Br. 34-38, 61-63. "Affirmance on an alternate ground is appropriate only when such affirmance does not depend on fact-finding." *Int'l Med. Prosthetics Research Assocs., Inc. v. Gore Enter. Holdings, Inc.*, 787 F.2d 572, 573 n.2 (Fed. Cir. 1986); *see also Hydril Co. LP v. Grant Prideco LP*, 474 F.3d 1344, 1351 (Fed. Cir. 2007) (declining to affirm where the parties "sharply dispute" the "complex and difficult questions" that would have to be resolved on remand). Here, as it did below before the Board, IBS sharply disputes Illumina's factual claims supporting its alternative arguments. Because the Board never addressed these alternative grounds and they are intensely factual, the Court should decline to consider them.

A. Zavgorodny's Azidomethyl Group Would Have Reasonably Been Expected to Meet Tsien's and Ju's Requirements

Illumina argues that an ordinary artisan would not have been motivated to use an azidomethyl group because as a factual matter he or she would not have expected it to be accurately and efficiently incorporated by a polymerase. Illumina Br. at 34-35. First, Illumina's argument is irrelevant because it relies on a

statement in Ju that is limited to *ester* linkages, not *ether* linkages such as the linkage at issue here. JA733 at 3:13-20; JA2348-50 at ¶¶ 25-27. Second, Illumina's argument is not supported by any evidence. Illumina relies on Canard even though Canard only suggests that an azido group "may also receive a nucleophilic attack" by a polymerase. JA3058. However, Canard does not present any evidence that an azido group would receive a nucleophilic attack, and both parties' experts agree that they are unaware of any such evidence. JA1573 ll. 7-16; JA2349 at ¶ 26. Third, Illumina ignores the fact that Canard is discussing the ***location*** of the central nitrogen of an azido group directly attached to the 3′ carbon – not an azidomethyl group attached to a 3′ oxygen. JA7312 at ll. 5-22; JA3058. Thus, a person of ordinary skill would understand that Canard's statement would not apply to Zavgorodny's 3′-O-azidomethyl group because the central nitrogen is in a different location. As Illumina's expert explained, in an enzyme-mediated reaction, the position of the electrophile would be critical for reactivity. JA1570 at l. 20 to JA1571 at l. 7.

Next, Illumina argues that Zavgorodny's conditions would not have been suitably mild for Tsien's sequencing purposes because Zavgorodny's cleavage conditions would denature DNA (i.e., separate the DNA strands).[10] Illumina Br. at

[10] Illumina asserts that the "Board found persuasive Illumina's 'evidence that an ordinary artisan would not have considered Zavgorodny's conditions suitably mild for Tsien's sequencing purposes.'" Illumina Br. at 17, 20. ***Not true.*** The

36-37. Illumina's expert relies on two references for his position that pyridine would denature the DNA templates of Ju and Tsien – Kit and Lee. JA2955-56 at ¶ 55. As IBS argued to the Board, neither reference stands for the proposition that Zavgorodny's conditions would denature DNA. Lee is not even directed to DNA denaturation. JA2360-61 at ¶¶ 40-42. Although Kit states that pyridine is a DNA denaturant, Illumina fails to acknowledge that Kit (and the references it cites) teaches that DNA denaturation depends on temperature and pH. JA2354-58 at ¶¶ 33-36. Indeed, the research group cited by Kit showed experimental examples of DNA remaining completely stable in the presence of organic solvents when the temperature was below 70ºC. JA2356-58 at ¶¶ 35-36. Notably, Zavgorodny taught cleaving at 20ºC and at an estimated pH of 10.1 which would not have been expected to denature DNA. JA2358-60 at ¶¶ 37-38; JA861. Indeed, Tsien itself actually ***proposes*** the use of pyridine for deblocking. JA1028 at ll.30-34.[11]

Board did not rule on this issue. Rather, the Board merely noted that in view of Illumina's evidence that Zavgorodny's conditions were not mild, IBS presented evidence that an ordinary artisan was not limited to Zavgorodny's specific conditions. JA14-15. As discussed herein, IBS also presented evidence that Zavgorodny's conditions were suitable for Tsien's methods.

[11] Illumina also argues that Zavgorodny's conditions would interfere with reinitiation of cDNA synthesis due to denaturation and thus not meet another one of Tsien's requirements. Illumina Br. at 37. As IBS argued to the Board but the Board did not address, because Zavgorodny's conditions would not be expected to denature DNA or interfere with sequencing, this argument also fails. JA2358-60 at ¶¶ 37-38; JA861.

Finally, Illumina argues that Zavgorodny's "complex, multi-step reaction" for cleavage would not meet Tsien's requirement for rapid and quantitative removal of the 3′-protecting group. Illumina Br. at 37. Zavgorodny's process involves two steps. JA1892 at ¶ 14. First, as previously discussed, Zavgorodny's conditions would have been expected to be quantitative. *See supra*, Section III.A. Second, Zavgorodny's conditions would have been expected to be rapid. Loubinoux (which Illumina's expert identified as the most relevant reference) provides that the second step of Zavgorodny's cleavage reaction would proceed "very rapidly." JA972; JA1897 at ¶ 24. Regarding the first step, IBS's expert explained that a person of ordinary skill in the art would not be dissuaded by the efficiencies of the prior art publications relied on by Illumina's expert because none of these publications take into account the teachings of Ju and Tsien. JA1898 at ¶ 25. Unlike those publications, Ju's and Tsien's methods allow for the use of very high concentrations of cleaving agent, thus increasing the speed and efficiency of the reaction. JA1898-99 at ¶¶ 25-26.

B. Illumina's Secondary Considerations Do Not Render the Claims Non-Obvious

Illumina's brief on appeal asserts that it presented evidence of objective indicia of non-obviousness that the Board did not address, but that further supports the Board's determination. Illumina Br. at 61-63. Illumina's alleged evidence does not save the claims from being obvious.

Neither now nor below to the Board has Illumina shown that its evidence of secondary considerations is "commensurate in scope with the claims which the evidence is offered to support." *MeadWestvVaco Corp. v. Rexam Beauty and Closures, Inc.*, 731 F.3d 1258, 1265 (Fed. Cir. 2013). Here, Illumina's secondary considerations hinge on the use of an azidomethyl protecting group in sequencing methods. For example, Illumina argues that it "satisfied a long-felt need in the industry for protecting groups that could be rapidly and efficiently cleaved under conditions compatible with DNA sequencing." Illumina Br. at 62. However, the claims are directed to a "method of labeling a nucleic acid molecule" and are not limited to DNA sequencing, much less a fast and efficient method for DNA sequencing. JA47 at claim 1. In fact, the challenged claims require the incorporation of only a single nucleotide, and do not even require the removal of the azido protecting group. JA1901 at ¶ 31-32; JA7.

Illumina also argues that its "azidomethyl protecting group performed unexpectedly better than the other protecting groups." Illumina Br. at 62. Again, its evidence is not commensurate in scope with the claims. To the contrary, Illumina's evidence of allegedly unexpected cleavage efficiency is based on a particular set of experimental cleavage conditions for a single 3′-O-azidomethyl deoxynucleotide. JA2967 at ¶ 78. The methods of the proposed claims, however, are much broader in scope, and encompass thousands of possible combinations of

different azido-comprising protecting groups, cleavage reagents, cleavage reagent concentrations, temperatures, etc. To the extent that Illumina relies on the *Nature* publication, any unexpected or surprising results cannot be attributed solely to the azidomethyl protecting group. JA3140-46, JA2365-68 at ¶¶ 48-51; *see also Intelligent Bio-Systems*, 2014 WL 3736339, *15-16 (rejecting Illumina's secondary considerations argument because it did not show that the stated results were attributable to the claimed nucleotide, rather than the cleaving reagents or other cleaving conditions); *Intelligent Bio-Systems*, 2014 WL 5490579, *15 (same).

Moreover, Illumina's evidence comparing the allyl protecting group to the azidomethyl protecting group is misleading. JA1899-1900 at ¶¶ 27-28. Whereas Illumina used a ***million-fold*** excess of cleaving reagent for its azidomethyl experiment, it only used an equivalent or slight access of cleaving agent for its allyl experiment. JA2964-66 at ¶¶ 69-74; JA1899-1900 at ¶ 28. A person of ordinary skill would expect that increasing the equivalents of the cleaving agent would increase the speed and efficiency of the cleavage reaction. JA1899-1900 at ¶ 28.

Illumina also asserts that its azidomethyl protecting groups were adopted and copied by Dr. Ju of Columbia. Illumina Br. at 62. IBS contested this fact issue of copying below, and it contests it now. First, Dr. Ju first published his use of azido protecting groups for a DNA sequencing method that was a hybrid of SBS and Sanger sequencing, and that would not fall within the scope of the '537 patent

claims. JA4911. Second, "copying requires evidence of efforts to replicate a specific product." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). Illumina does not and cannot claim that Dr. Ju copied an actual Illumina product (such as its nucleotides used in its sequencers). Moreover, Dr. Ju's publications specifically credit Zavgorodny with developing the azidomethyl protecting group. *See, e.g.*, JA4912 ("In 1991, Zavgorodny *et al.* (25) reported the capping of the 3′-OH group of the nucleoside with an azidomethyl moiety, which can be chemically cleaved under mild condition [sic] with triphenylphosphine."). Thus, this court should decline to consider fact issues of secondary considerations that the Board did not, and that in any event, do not support the Board's decision regarding the patentability of the claims.

CONCLUSION

The court should reverse the Board's decision. In the alternative, the court should vacate and remand for further proceedings.

Dated: November 24, 2015

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CERTIFICATE OF SERVICE

In accordance with Federal Rule of Appellate Procedure 25 and Federal Circuit Rule 25, I certify that on this date November 24, 2015, I caused the foregoing to be served via the court's CM/ECF system and electronic mail on the principal attorneys for each party.

Dated: November 24, 2015

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 6,217 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b). As permitted by Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned has relied upon the word count feature of Microsoft Word 2010 in preparing this certificate.

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Times New Roman font.

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